REMARKS

Claims 1-15 were pending prior to this Response. By the present communication, claim 15 has been cancelled without prejudice and new claims 16 and 17 have been added. In addition claims 1, 4-8, and 13 have been amended to claim Applicants' invention with greater particularity. The claim amendments add no new matter, being fully supported by the Specification and original claims. Accordingly, claims 1-14 and 16-17 are currently pending in this application.

The Sequence Listing

Applicants respectfully traverse the assertion in the Office Action that this application fails to comply with the requirements of 37 C.F.R. §1.821 through § 1.825 due to failure to use a sequence identifier for the EcoRI linker sequence on page 25 in paragraph [0077] and the requirement for submission of a computer readable sequence listing, a paper sequence listing, and a statement that the content of the paper and computer readable copies are the same and include no new matter to introduce the sequence of the EcoRI linker.

M.P.E.P 2422.01 *Definitions of Nucleotide and/or Amino Acids for Purpose of Sequence Rules – 2400 Biotechnology*, defines the sequences to which 37 CFR 1.821 through 1.825 apply as follows: "Nucleotide and/or Amino acid sequences as used in 37 CFR 1.821 through 1.825 are interpreted to mean an unbranched sequence of four or more amino acids or an unbranched sequence of ten or more nucleotides." In the present case, the Eco RI linker sequence on page 27 of the application contains only eight nucleotides. Applicants respectfully submit that M.P.E.P 2422.01 excludes such short sequences from the requirements under 37 C.F.R. §1.821 through § 1.825. With regard to the sequences designated as SEQ ID NO:1 and SEQ ID NO:2,

Applicants submitted a Request for permission to use the sequence listing of a parent application on January 18, 2002. Accordingly, Applicants respectfully request reconsideration and withdrawal of the requirement for Applicants to provide a sequence identifier for the EcoRI linker sequence and to submit a computer readable sequence listing, a paper sequence listing, and a statement that the content of the paper and computer readable copies are the same and include no new matter for the present application.

Drawings

The Office Action further indicates that the drawings are objected to. In particular, Figure 7 is objected to for misspelling of "fluor, Figure 14 is objected to for use of the term "from host" in place of the phrase "the library", and Figure 15 is objected to formisspelling of the term "growth". To overcome the objection to the drawings, Applicants submit herewith as Exhibit A new formal drawings for Figures 7, 14 and 15 that contain corrections for the three items above. Accordingly, Applicants respectfully request reconsideration and withdrawal of the objection to the drawings.

The Objection to the Specification

Applicants have addressed the objection to the Specification for alleged informalities in the Office Action by introducing the following amendments:

Correction of misspelling of "Nucleic" in the Abstract;

Replacement of a "(" by a missing Greek character at the following paragraph numbers: 0045, 0082, 0136, 0147, and 0148;

Deletion of reference to "Figure X" in paragraph 0185;

Correction of typographical errors to replace "the" by "then" at paragraph 0185; to replace "grown" by "growth" at paragraph 0189; to correct a grammatical error in the phrase "compounds can be utilized" at paragraph 0197;

Replacement of misaligned Table and correction of typographical error in paragraph 0214;

Restatement of Related References on pages 69-70 so that each reference starts a new paragraph (paragraphs 0238-0257); and

Replacement of the title of the invention by a title more descriptive of the invention: A METHOD FOR HIGH THROUGHPUT SCREENING OF AN ENVIRONMENTAL LIBRARY.

In view of the above amendments to the Specification to correct informalities, Applicants respectfully request reconsideration and withdrawal of the Objection to the Specification.

The Objections to the Claims

Applicants respectfully traverse the objections to the claims for allegedly containing informalities. With regard to claim 1, the Examiner alleges that the abbreviation "FACS" as used therein introduces an informality, which Applicants have overcome by defining the abbreviation as "fluorescence activated cell sorting" at its first recitation in the claim set, as requested by the Examiner.

With regard to claim 15 in light of the recitation in independent claim 1 of FACS, the Examiner alleges that recitation of markers that could be considered as non-fluorescent markers is an informal use of dependent claim format due to failure to further limit the subject matter of the independent claim. However, Applicants have cancelled claim 15 without prejudice, rendering the rejection moot as to claim 15.

In view of the amendment to claim 1 and cancellation of claim 15, Applicants submit that all pending claims are free of informalities and reconsideration and withdrawal of the rejection are respectfully requested.

The Rejection under 35 U.S.C. § 112, First Paragraph

Applicants respectfully traverse the rejection of claim 10 under 35 U.S.C. § 112, First Paragraph for alleged failure to provide a description of the invention commensurate with the claim scope. While the rejection initially refers to claim 10, it appears that the Examiner intended the rejection to pertain to claim 1 (which is mentioned later in the rejection). Applicants respectfully disagree with the Examiner's assertion that the Specification provides support only for a single species of membrane bound G-protein receptors and ligands and does not describe the claimed genus of first and second test proteins in such full, clear, concise and exact terms as to indicate that Applicants had possession at the filing of the application of the invention as claimed.

The Examiner incorrectly relies upon the "Written Description" Requirement published in the Federal Register (Volume 66, Number 4, pages 1099-1111) because this document pertains to description necessary to support generic claims to families of amino acid sequences and nucleic acid sequences rather than to assay methods. Applicants submit that the crux of the present invention is fluorescence screening of *environmental libraries* expressed in *prokaryotic* cells using "two-hybrid" screening methodology. Two-hybrid screening assays were well known in the art at the filing at the present application, as evidence by K.H. Young, "Two-Hybrid: So Many Interactions, (in) So Little Time . . ."(of record herein), but use of such assays to screen environmental libraries of naturally occurring molecules in prokaryotic cells was not known.

In the present application, Applicants use the membrane bound G-protein/ligand system to illustrate the invention. Applicants also teach that a broader category of molecules is

"functional transducing proteins" of which G-proteins are only an example (Specification, Paragraphs 0173—0175). It is well settled law, that an Applicant's claims are not to be limited to the scope of the examples, and Applicants respectfully submit that to limit the claims to the membrane bound G-protein/ligand system is to limit the invention to the examples used to illustrate the invention. In addition, Applicants submit that in support of the rejection the Examiner has presented no reason for assuming that the functional predictability of the assay depends upon the structure of the test proteins attached to the DNA binding moiety and transcriptional activation moiety.

In addition, it is not a deciding factor that the terms "first protein" and "second protein" are not used to describe the invention in the Specification: "Adequate description under the first paragraph of 35 U.S.C. 112 does not require literal support for the claimed invention. . . . Rather, it is sufficient if the originally-filed disclosure would have conveyed to one having ordinary skill in the art that an appellant had possession of the concept of what is claimed" ***Ex parte Parks***, 30 USPQ 2d 1234, 1236–37 (B.P.A.I. 1993). Applicants respectfully submit that, in view of the knowledge of the art concerning the use of two hybrid assay systems, those of skill in the art would have understood that Applicants were in possession of the concept of using fluorescence screening of *environmental libraries* expressed in *prokaryotic* cells for two hybrid interaction screening of the full range of molecules that could be expressed when brought together by a DNA binding moiety and transcriptional activation moiety.

Accordingly, Applicants submit that the written description requirement under 35 U.S.C. § 112, First Paragraph, is fully met by the Specification describing the invention. Therefore, reconsideration and withdrawal of the rejection are respectfully requested.

The Rejection under 35 U.S.C. § 112, Second Paragraph

Applicants respectfully traverse the rejection of claims 1-15 under 35 U.S.C. § 112, Second Paragraph, as allegedly lacking in definiteness. With regard to claim 1, the Examiner asserts that "the method steps do not achieve the intended goal of the method" as set forth in the preamble (Office Action, page 9). To clarify an inherent connection between the preamble and method steps, claim 1 has been amended to recite that modulation of expression results in a change in fluorescence of the microenvironment, which modulation indicates the agent enhances or inhibits expression of the fluorescent protein. Applicants respectfully submit that this amendment clarifies the connection between the intended goal described in the preamble and the method steps of the claim.

With regard to claim 4, the Examiner asserts that the phrase "the agent inhibits the activity of the first protein or the second protein" is unclear because the parent claim is directed to screening for an agent that modulates interaction, not for an agent that inhibits activity. To clarify claim 4, the phrase cited by the Examiner has been replaced by the phrase "the modulation inhibits the expression of the first protein or the second protein," thereby matching the recited limitation of claim 4 with the goal recited in claim 1.

With regard to claim 5, the Examiner also asserts that the phrase "the agent enhances the activity of the first protein or the second protein" is unclear because the parent claim is directed to screening for an agent that modulates interaction, not for an agent that enhances activity. To clarify claim 5, the phrase cited by the Examiner has been replaced by the phrase "the modulation enhances the expression of the first protein or the second protein", thereby matching the recited limitation of claim 5 with the goal recited in claim 1.

With regard to claim 6, the Examiner asserts that the limitations "the recombinant cell" and "the target protein and detectable marker" introduce vagueness due to a lack proper antecedent basis. For clarity, claim 6 has been amended to recite "wherein the recombinant

prokaryotic cell expressing the agent is co-encapsulated with a second recombinant cell expressing the fluorescent protein," thus clarifying that antecedent basis is provided in claim 1 for "the recombinant prokaryotic cell."

With regard to claims 7 and 8, the Examiner asserts that it is unclear to which of the two recombinant cells the phrase "the recombinant cell" refers. According, claims 7 and 8, which each depend from claim 6, have each been amended to clarify that the phrase at issue pertains to the "second" recombinant cell (i.e., the cell expressing the fluorescent protein).

With regard to claim 13, the Examiner asserts that it is unclear how FACS can be used with non-fluorescent materials, such as a visible dye, a chemiluminescent material, and the like. To clarify this point, claim 13 has been amended to depend upon claim 6 and recite "the fluorescent protein is a fluorescent dye, a bioluminescent material, a chemiluminescent material, or a fluorescent enzymatic substrate," thereby clarifying that all signaling entities are fluorescent, as required by claim 1.

In view of the above amendments and remarks, Applicants respectfully submit that claims 1-14 and new claims 16 and 17 meet all requirements under 35 U.S.C. § 112, Second Paragraph, and reconsideration and withdrawal of the rejection are respectfully requested.

The Rejections Under 35 U.S.C. 102(b) and 103

A. Applicants respectfully traverse the rejection of claims 1, 7, 9, 13 and 15 under 35 U.S.C. § 102(b) as allegedly being anticipated by, or in the alternative, under 35 U.S.C. § 103 as allegedly being unpatentable over Mendelsohn et al (*Current Opinion in Biotechnology* (1994) 5:482-485; hereinafter "Mendelsohn"). Claim 15 has been cancelled rendering the rejection moot as to claim 15. Applicants respectfully submit that the invention methods for screening for an agent that modulates the interaction of a first test protein linked to a DNA binding moiety and a second test protein linked to a transactional activator, as defined by amended claim 1, distinguish over the disclosure of Mendelsohn at least by requiring that an environmental library of naturally occurring DNA obtained from a mixed population (i.e. different species) of organisms is expressed for the screening in prokaryotic host cells.

By contrast Mendelsohn is absolutely silent regarding expression of library cells in prokaryotic cells for use in a two-hybrid system. The Examiner points out that Mendelsohn discloses the use of two-hybrid systems in either yeast or mammalian cells. However, expression of library molecules in prokaryotic cells is neither disclosed nor suggested by Mendelsohn. Therefore, Mendelsohn fails to disclose or suggest each and every element of the invention methods, as recited by amended claim 1, as would be required to establish anticipation. Applicants respectfully submit, therefore, that claims 1, 7, 9, and 13 as well as new claims 16 and 17 are not anticipated by Mendelsohn and reconsideration and withdrawal of the rejection are respectfully requested.

In the alternative, Applicants respectfully submit that Mendelsohn itself does not suggest how to conduct a two-hybrid assay in prokaryotic cells. Moreover the Examiner has provided no reasons in support of an expectation of success in the art that such a procedure could be conducted wherein the library cells are expressed in prokaryotic cells. Therefore, Applicants

respectfully submit that claims 1, 7, 9, and 13 as well as new claims 16 and 17 are not prima facie obvious over the disclosure of Mendelsohn under 35 U.S.C. § 103 and reconsideration and withdrawal of the rejection for alleged unpatentability over Mendelsohn are respectfully requested.

B. Applicants respectfully traverse the rejection of claims 1-3, 5, 7, 9 and 13-15 under 35 U.S.C. §103(a) over Anderson et al. (U.S. Patent No. 5,968,738; hereinafter "Anderson") in view of Young et al. (Biology of Reproduction (1998 58:302-311; hereinafter "Young"). Claim 15 has been cancelled without prejudice rendering the rejection moot as to claim 15. Applicants respectfully submit that the invention methods for screening for an agent that modulates the interaction of a first test protein linked to a DNA binding moiety and a second test protein linked to a transactional activator, as defined by amended claim 1, distinguish over the combined disclosure of Anderson and Young, at least by requiring that an environmental library of naturally occurring DNA obtained from a mixed population (i.e. different species) of organisms is expressed for the screening in prokaryotic host cells.

By contrast, neither Anderson nor Young mention expression of an environmental library of cells obtained from a mixed population of cells in prokaryotic cells for use in a two-hybrid system. The Examiner points out that Anderson discloses the use of two-hybrid systems in mammalian cells. However, expression of library molecules in prokaryotic cells is neither disclosed nor suggested by Anderson. In fact, Anderson's focus on GFP mutations that will function in eukaryotic systems suggests that eukaryotic systems are needed for two-hybrid screening.

Young fails to cure this deficiency in Anderson because Young focuses entirely on two-hybrid screening systems utilizing yeast cells. Moreover, the Examiner has provided no evidence that those of skill in the art would have had a reasonable expectation that an environmental

library of naturally occurring DNA obtained from a mixed population (i.e. different species) of organisms could be expressed in prokaryotic cells when coencapsulated in a microenvironment for fluorescence screening of a two-hybrid system.

Accordingly, Applicants respectfully submit that *prima facie* obviousness of the invention methods, as recited by amended claim 1, is not established under 35 U.S.C. § 103 by the combined disclosures of Anderson and Young, and reconsideration and withdrawal of the rejection are respectfully requested.

In view of the above amendments and remarks, Applicants submit that all objections and rejections of the claims have been overcome. If the Examiner would like to discuss any of the issues raised in the Office Action, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

Please charge any additional fees, or make any credits, to Deposit Account No. 50-1355.

Respectfully submitted,

Date: March 17, 2003

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Enclosure: Exhibit A -- New formal drawings for Figures 7, 14 and 15.